Application Serial No. 09/567,451 Group Art Unit 1615

EXHIBIT A CLAIMS WITH MARKINGS TO SHOW CHANGES

- 1. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
- (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
- (ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.
- 3. (Amended) A method of treatment of a patient's hypertension and/or angina comprising administration of a preparation of claim 1 [or 2] in the night to a patient for effect the next morning and which formulation exhibits a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given with food and without food according to the same FDA guidelines or criteria.
- 4. (Amended) The controlled-release Galenical preparation of claim 1 [or 2] wherein the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
- (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - (a) between about 1% and about 15% after 2 hours;
 - (b) between about 7% and about 35% after 4 hours;
 - (c) between about 30% and about 58% after 8 hours;

- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours.
- 5. (Amended) The controlled-release Galenical preparation of claim [1 or] 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
- into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - (a) between about 4% and about 8% after 2 hours;
 - (b) between about 16% and about 21% after 4 hours;
 - (c) between about 44% and about 52% after 8 hours;
 - (d) between about 69% and about 76% after 14 hours; and
 - and in excess of about 85% after 24 hours; (e)

into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- between about 4% and about 15% after 2 hours; (a)
- (b) between about 16% and about 30% after 4 hours;
- (c) between about 44% and about 62% after 8 hours;
- in excess of about 80% after 24 hours. (d)
- 6. (Amended) The preparation of claim [1, 2,] 4 [or 5] wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

- The preparation of claim [1, 2, 4, 5,] 6 [or 7] wherein the 8. (Amended) preparation is a diffusion controlled preparation.
- The preparation of claim [1, 2, 4,] 5[, 6, 7 or 8] wherein the 9. (Amended) preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.
- The preparation of claim [1, 2, 4, 5, 6, 7, 8 or] 9 in capsule form. 10. (Amended)
- 11. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8 or] 9 in tablet form.
- 12. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8,] 9[, 10 or 11] wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.
- The preparation of claim 13 wherein the wetting agent assists to 14. (Amended) maintain the solubility of the Diltiazem in each microgranule [bead], ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.
- The preparation of claim [12, 13 or] 14 wherein the membrane 15. (Amended) comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.
- 16. (Amended) The preparation of claim 12 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.

- 17. (Amended) The preparation of claim [12, 13, 14, 15 or] 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30D] and hydroxypropylmethylcellulose.
- 18. (Amended) The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule [bead], and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).
- 19. (Amended) The preparation of claim 13 [or 14] wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane [Eudragit RS, Eudragit RL] and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.
- 20. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8,] 9[, 10 or 11] wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.
- 21. (Amended) The preparation of claim 20 wherein the dissolution agent is an organic acid <u>comprising</u> [such as] adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid[,] <u>or</u> tartaric acid [and the like] which permits the diltiazem to dissolve in gastrointestinal fluids <u>even</u> when the microgranules pass into the [higher pH] regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.
- 41. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 120 mg of Diltiazem.

- 42. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 180 mg of Diltiazem.
- 43. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 17 or 17] wherein the preparation contains 240 mg of Diltiazem.
- 44. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 300 mg of Diltiazem.
- 45. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 360 mg of Diltiazem.
- 46. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 420 mg of Diltiazem.
- 48. (Amended) The preparation of claim [12, 13, 14, 15, 16,] 17[, 18 or 19] wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C₁₂ to C₂₀ fatty acid esters of saccarose, including [commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.) such as] sucrose stearate [marketed under the trade name of Crodesta];

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene [(Brijs, Renex and Eumulgines, Henkel, RFA)];

sorbitan fatty acid esters [(Span, Atlas, U.S.A.)];

polyglycides-glycerides and polyglycides-alcohols esters [(Gelucires, Gattefosse, France)]

Metal salts [such as NaCl or sodium lauryl sulphate].

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The preparation of claim 12 wherein the wetting agent is in 49. (Amended) association with the diltiazem in the microgranule [bead] and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [such as Eudragit NE30D] enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

- 52. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustainedrelease dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
- a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
- bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent [The preparation of claim 12, 13, 14, 15, 16, 17, 18, 19, 48 or 49] in which the core and membrane comprise:

		%W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101))8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0

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(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid	
	ethyl ester and acrylic acid methyl ester	
	[Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

54. (Amended) The preparation of claim 12[, 13, 14, 15, 16, 17, 18, 19, 48 or 49] in which the core and membrane comprise:

- (i) in the core,
 - (a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

- (ii) in the membrane,
 - (c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

56. (Amended) The preparation of claim 12[, 13, 14, 15, 16, 17, 18, 19, 48 or 49] in which the core and membrane comprise:

(i) in the core,

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- (a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
- (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

- (ii) in the membrane,
 - (c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.
- 58. (Amended) The preparation of claim 12[, 13, 14, 15, 16, 17, 18, 19, 48 or 49] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.
- 59. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

60. (Amended) The controlled-release Galenical preparation of claim [1 or] 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

- (i) in the core,
 - (a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

- (ii) in the membrane,
 - (c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.
- 63. (Amended) The preparation of claim 60[, 61 or 62] wherein the core and membrane comprise:
 - (i) in the core,

- (a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
- (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

- (ii) in the membrane,
 - (c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - between about 7% and about 11% (% w/w of the preparation) (d) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.
- 64. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustainedrelease dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
- a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
- bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time

wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

in the core, (i)

- between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; <u>and</u>
- (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

in the membrane, (ii)

- between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
- between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

[The preparation of claim 60, 61 or 62] wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b) .	Microcrystalline cellulose (Avicel ph101)8 - 9.5	
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5

(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid	
	ethyl ester and acrylic acid methyl ester	
	[Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

- 65. (Amended) The preparation of claim 60[, 61, 62, 63 or 64] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.
- 66. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 60[, 61, 62, 63, 64 or 65] to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 67. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustainedrelease dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
- into an aqueous medium at the following rates measured using the method of (i) United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - (a) between about 1% and about 15% after 2 hours;

- between about 7% and about 35% after 4 hours; (b)
- (c) between about 30% and about 58% after 8 hours;
- between about 55% and about 80% after 14 hours; and (d)
- (e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- between about 7% and about 45% after about 4 hours; (b)
- between about 30% and about 68% after about 8 hours; (c)
- in excess of about 75% after about 24 hours. (d)
- A controlled-release Galenical preparation of pharmaceutically 68. (Amended) acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
- into an aqueous medium at the following rates measured using the method of (i) United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - between about 4% and about 8% after 2 hours; (a)
 - between about 16% and about 21% after 4 hours; (b)
 - (c) between about 44% and about 52% after 8 hours;
 - between about 69% and about 76% after 14 hours; and (d)
 - and in excess of about 85% after 24 hours; (e)

into a buffered medium having a pH about 5.8 at the following rates and/or (ii) measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

between about 4% and about 15% after 2 hours; (a)

- (b) between about 16% and about 30% after 4 hours;
- (c) between about 44% and about 62% after 8 hours;
- (d) in excess of about 80% after 24 hours.
- 69. (Amended) The preparation of claim [67 or] 68 wherein the Cmax of Diltiazem in the blood is obtained between about 11 about 13 hours after administration of the preparation.
- 70. (Amended) The preparation of claim [67,] 68 [or 69] wherein the Diltiazem is in the form of Diltiazem HCl.
- 71. (Amended) The preparation of claim [67,] 68[, 69 or 70] wherein the preparation is a diffusion controlled preparation.
- 72. (Amended) The preparation of claim [67,] 68[, 69, 70 or 71] wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.
- 73. (Amended) The preparation of claim [67,] 68[, 69, 70, 71 or 72] in capsule form.
- . 74. (Amended) The preparation of claim [67,] 68[, 69, 70, 71 or 72] in tablet form.
- 75. (Amended) The preparation of claim 67[, 68, 69, 70, 71, 72, 73 or 74] wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.
- 77. (Amended) The preparation of claim 76 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each <u>microgranule</u> [bead], ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

- The preparation of claim [75, 76 or] 77 wherein the membrane 78. (Amended) comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer) of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.
- The preparation of claim 75 wherein the preparation comprises 79. (Amended) a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.
- The preparation of claim [75, 76,] 77[, 78 or 79] wherein the 80. (Amended) membrane comprises Eudragit NE30D and hydroxypropylmethylcellulose.
- 81. (Amended) The preparation of claim 80 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule [bead], and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).
- The preparation of claim [76 or] 77 wherein the Diltiazem is 82. (Amended) mixed with the wetting agent and the membrane comprises an acrylic polymer [Eudragit RS, Eudragit RL] and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.
- The preparation of claim [67,] 68[, 69, 70, 71, 72, 73 or 74] 83. (Amended) wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof

associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

84. (Amended) The preparation of claim 83 wherein the dissolution agent is an organic acid <u>comprising</u> [such as] adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid[,] <u>or</u> tartaric acid [and the like] which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the [higher pH] regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

103. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 120 mg of Diltiazem.

104. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 180 mg of Diltiazem.

105. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 240 mg of Diltiazem.

106. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 300 mg of Diltiazem.

107. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 360 mg of Diltiazem.

108. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 420 mg of Diltiazem.

110. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which

the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

between about 4% and about 8% after 2 hours; (a) between about 16% and about 21% after 4 hours; (b) between about 44% and about 52% after 8 hours; (c) between about 69% and about 76% after 14 hours; and (d) and in excess of about 85% after 24 hours; (e)

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- between about 4% and about 15% after 2 hours; (a)
- between about 16% and about 30% after 4 hours; (b)
- between about 44% and about 62% after 8 hours; (c)_
- (d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, [The preparation of claim 75, 76, 77, 78, 79, 80, 81 or 82] wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins:

 C_{12} to C_{20} fatty acid esters of saccarose, commercialized under the name of sucroesters [(Gattefosse, France)] or under the name of crodesters [(Croda, U.K.)] such as sucrose stearate marketed under the trade name of Crodesta; xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene [(Brijs, Renex and Eumulgines, Henkel, RFA)];

sorbitan fatty acid esters [(Span, Atlas, U.S.A.)];

polyglycides-glycerides and polyglycides-alcohols esters [(Gelucires, Gattefosse, France)]

Metal salts [such as NaCl or sodium lauryl sulphate].

The preparation of claim 75 wherein the wetting agent is in 111. (Amended) association with the diltiazem in the microgranule [bead] and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [such as Eudragit NE30D] enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

- 114. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
- into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
- between about 4% and about 8% after 2 hours; (a) (b) between about 16% and about 21% after 4 hours; between about 44% and about 52% after 8 hours; (c) (d) between about 69% and about 76% after 14 hours; and and in excess of about 85% after 24 hours; (e)

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

between about 4% and about 15% after 2 hours;

between about 16% and about 30% after 4 hours; (b) between about 44% and about 62% after 8 hours; (c)

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in excess of about 80% after 24 hours, wherein the preparation (d) comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, [The preparation of claim 75, 76, 77, 78, 79, 80, 81, 82, 110 or 111] in which the core and membrane comprise:

		. %W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
.(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
· (g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl	
	ester and acrylic acid methyl ester	
	[Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

116. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of		
United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:		
(a) between about 4% and about 8% after 2 hours;		
(b) between about 16% and about 21% after 4 hours;		
(c) between about 44% and about 52% after 8 hours;		
(d) between about 69% and about 76% after 14 hours; and		
(e) and in excess of about 85% after 24 hours;		
·		
and/or (ii) into a buffered medium having a pH about 5.8 at the following rates		
measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in		
900ml of the buffered medium:		
(a) between about 4% and about 15% after 2 hours;		
(b) between about 16% and about 30% after 4 hours;		
(c) between about 44% and about 62% after 8 hours;		
(d) in excess of about 80% after 24 hours, wherein the preparation		
comprises a plurality of microgranules, each microgranule comprising a central core		
containing the form of diltiazem coated with a microporous membrane and the		
central core comprises Diltiazem or pharmaceutically acceptable salt thereof		
associated with a wetting agent, [The preparation of claim 75, 76, 77, 78, 79, 80, 81,		
82, 110 or 1111 in which the core and membrane comprise:		

- (i) in the core,
 - between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - between about 2% and about 25% wetting agent (% w/w of the (b) total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

- between about 0.1% and about 2% of the total preparation of (c) water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
- between about 5% and about 20% (% w/w of the preparation) (d) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.
- A controlled-release Galenical preparation of pharmaceutically 118. (Amended) acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
- into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
- between about 4% and about 8% after 2 hours; (a) (b) between about 16% and about 21% after 4 hours; between about 44% and about 52% after 8 hours; (c) (d) between about 69% and about 76% after 14 hours; and (e) and in excess of about 85% after 24 hours;
- and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:
- between about 4% and about 15% after 2 hours;
- (b) between about 16% and about 30% after 4 hours;
 - (c) between about 44% and about 62% after 8 hours;
- in excess of about 80% after 24 hours, wherein the preparation (d) comprises a plurality of microgranules, each microgranule comprising a central core

containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, [The preparation of claim 75, 76, 77, 78, 79, 80, 81, 82, 110 or 111] in which the core and membrane comprise:

- (i) in the core,
 - (a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

- (ii) in the membrane,
 - (c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.
- 120. (Amended) The preparation of claim [75, 76,] 77[, 78, 79, 80, 81, 82, 110 or 111] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.
- 122. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable. Diltiazem including the pharmaceutically acceptable salts thereof,

suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustainedrelease dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof . associated with a wetting agent in which the core and membrane comprise:

- (i) in the core,
 - between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - between about 2% and about 25% wetting agent (% w/w of the (b) total preparation);

- (ii) in the membrane,
 - (c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

- 125. (Amended) The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:
 - (i) in the core,
 - (a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

- (ii) in the membrane,
 - (c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.
- 127. (Amended) The preparation of claim 122[,] or 124[, 125 or 126] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.
- 128. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 122, 123[,] or 124[, 125, 126 or 127] to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.



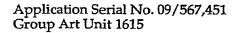


EXHIBIT B CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT

- 1. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
- (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
- (ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.
- 2. The controlled release Galenical preparation of claim 1 wherein the higher bioavailability achieved after night administration of the preparation than morning administration without food exceeds $25\% C_{max}$.
- 3. (Amended) A method of treatment of a patient's hypertension and/or angina comprising administration of a preparation of claim 1 in the night to a patient for effect the next morning and which formulation exhibits a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given with food and without food according to the same FDA guidelines or criteria.
- 4. (Amended) The controlled-release Galenical preparation of claim 1 wherein the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem



- into an aqueous medium at the following rates measured using the method of (i) United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - (a) between about 1% and about 15% after 2 hours;
 - between about 7% and about 35% after 4 hours; (b)
 - between about 30% and about 58% after 8 hours; (c)
 - between about 55% and about 80% after 14 hours; and (d)
 - and in excess of about 75% after 24 hours. (e)

into a buffered medium having a pH between about 5.5 and about 6.5, and/or (ii) at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- between about 1% and about 25% after about 2 hours; (a)
- between about 7% and about 45% after about 4 hours; (b)
- between about 30% and about 68% after about 8 hours; (c)
- in excess of about 75% after about 24 hours. (d)

5. (Amended) The controlled-release Galenical preparation of claim 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

- into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - between about 4% and about 8% after 2 hours; (a)
 - between about 16% and about 21% after 4 hours; (b)
 - between about 44% and about 52% after 8 hours; (c)
 - between about 69% and about 76% after 14 hours; and (d)
 - (e) and in excess of about 85% after 24 hours;

into a buffered medium having a pH about 5.8 at the following rates and/or (ii) measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- between about 4% and about 15% after 2 hours; (a)
- between about 16% and about 30% after 4 hours; (b)
- between about 44% and about 62% after 8 hours; (c)



(d) in excess of about 80% after 24 hours.

- 6. (Amended) The preparation of claim 4 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.
- The preparation of claim 1, 2, 4, 5 or 6 wherein the Diltiazem is in the form of Diltiazem HCl.
- 8. (Amended) The preparation of claim 6 wherein the preparation is a diffusion controlled preparation.
- 9. (Amended) The preparation of claim 5 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.
- 10. (Amended) The preparation of claim 9 in capsule form.
- 11. (Amended) The preparation of claim 9 in tablet form.
- 12. (Amended) The preparation of claim 9 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.
- 13. The preparation of claim 12 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.



14. (Amended) The preparation of claim 13 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

- 15. (Amended) The preparation of claim 14 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.
- 16. (Amended) The preparation of claim 12 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.
- 17. (Amended) The preparation of claim 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

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- 18. (Amended) The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).
- 19. (Amended) The preparation of claim 13 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.
- 20. (Amended) The preparation of claim 9 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

- 21. (Amended) The preparation of claim 20 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.
- 22. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 1 or 2 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 23. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 4 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 24. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 25. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 6 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 26. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 27. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

- 28. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 29. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 10 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 30. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 31. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 32. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 33. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 34. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

- 35. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 16 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 36. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 37. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 38. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 19 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 39. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 20 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 40. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 21 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.



41. (Amended) The preparation of claim 5 wherein the preparation contains 120 mg of Diltiazem.

The preparation of claim 5 wherein the preparation contains 180 42. (Amended) mg of Diltiazem.

43. (Amended) The preparation of claim 5 wherein the preparation contains 240

mg of Diltiazem.

44. (Amended) The preparation of claim 5 wherein the preparation contains 300

mg of Diltiazem.

45. (Amended) mg of Diltiazem.

The preparation of claim 5 wherein the preparation contains 360

46. (Amended) The preparation of claim 5 wherein the preparation contains 420 mg of Diltiazem.

A method of treatment of a patient's hypertension and/or angina comprising 47. the administration of the preparation of Diltiazem of claim 41, 42, 43, 44, 45 or 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

The preparation of claim 17 wherein the wetting agent is 48. (Amended) selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

 C_{12} to C_{20} fatty acid esters of saccarose, including sucrose stearate;

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid ester;

polyglycides-glycerides and polyglycides-alcohols esters

Metal salts.



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49. (Amended) The preparation of claim 12 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

- 50. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 51. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 49 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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- 52. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans
- (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
- (ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core

comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

		/	70 VV / VV
	(a)	Diltiazem hydrochloride	69 - 73
	(b)	Microcrystalline cellulose (Avicel ph191)8 - 9	9.5
	(c)	Povidone K30	1-2
0 `	(d)	Sucrose stearate	7 - 8
<i>*</i>	(e)	Magnesium stearate NF	0.5 - 2.5
	(f)	Talc USP	0.5 - 5.0
	(g)	Titanium dioxide (USP)	0.15 - 0.3
	(h)	Hydroxypropylmethylcellulyse 2910	0.3 - 0.6
	(i)	Polysorbate 80 (tween)	0.01 - 0.025
	(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
	(k)	a neutral acrylic polymer of acrylic acid	
		ethyl ester and acrylic acid methyl ester	
		(dry of 30%)	7 - 11
		Purified water USP	0 (used for mixing)

53. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

54. (Amended) The preparation of claim 12 in which the core and membrane comprise:

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- (i) in the core,
 - (a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

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- between about 0.1% and about 2% of the total preparation of (c) water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
- between about 5% and about 20% (% w/w of the preparation) (d) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- A method of treatment of a patient's hypertension and/or angina 55. comprising the administration of the preparation of Diltiazem of claim 54 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 56. (Amended) The preparation of claim 12 in which the core and membrane comprise:
 - (i) in the core,

- between about 69% and about 73% (% w/w of the total (a) preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
- between about 7% and about 8% wetting agent (% w/w of the (b) total preparation);

together with suitable adjuvants; and

in the membrane, (ii)

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- between about 0.3% and about 0.6% of the total preparation of (c) water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
- between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- 57. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 58. (Amended) The preparation of claim 12 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads. which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.
- 59. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- The controlled-release Galenical preparation of claim 2 in which 60. (Amended) the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:
 - (i) in the core,

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- between about 50% and about 85% (% w/w of the total (a) preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
- between about 2% and about 25% wetting agent (% w/w of the (b) total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
 - between about 0.1% and about 2% of the total preparation of (c) water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- The preparation of claim 60 wherein the microgranules are in capsule form. 61.
- The preparation of claim 60 wherein the microgranules are in tablet form. 62.
- The preparation of claim 60 wherein the core and membrane 63. (Amended) comprise:
 - (i) in the core,

. . .

- between about 69% and about 73% (% w/w of the total (a) preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
- (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
 - (c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

64. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

- (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
- (ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:
 - (i) in the core,

- between about 50% and about \$5% (% w/w of the total (a) preparation) of Diltiazem or pharmaceufically acceptable salt thereof;
- between about 2% and about 25% wetting agent (% w/w of the (b) total preparation);

together with suitable adjuvants; and

- in the membrane, (ii)
 - between about 0.1% and about 2% of the total preparation of (c) water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - between about 5% and about 20% (% w/w of the preparation) (d) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, togethef with suitable adjuvants,

wherein the core and membrane domp

	. /	% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)8 - 9	2.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate (crodesta F150)	7-8
(e)	Magnesium stearate NF/	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USF)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid	
	ethyl ester and acrylic acid methyl ester	
	(dry of 30%)	7 - 11

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Purified water USF

U (used for mixing).

65. (Amended) The preparation of claim 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

66. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 60 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

67. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 1% and about 15% after 2 hours;
- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55%, and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

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- between about 7% and about 45% after about 4 hours; (b)
- between about 30% and about 68% after about 8 hours; (c)
- in excess of about 75% after about 24 hours. (d)
- A controlled-release Galenical preparation of pharmaceutically 68. (Amended) acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10/hours and about 15 hours (Tmax) after administration, the preparation being in a/sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
- into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - between about 4% and about 8% after 2 hours; (a)
 - between about 16% and about 21% after 4 hours; (b)
 - between about 44% and about 52% after 8 hours; (c)
 - between about 69% and about 76% after 14 hours; and (d)
 - and in excess of about 85% after 24 hours; (e)

into a buffered medium having a pH about 5.8 at the following rates and/or (ii) measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- between about 4% and about 15% after 2 hours; (a)
- between about/16% and about 30% after 4 hours; (b)
- between about 44% and about 62% after 8 hours; (c)
- in excess of about 80% after 24 hours. (d)
- 69. (Amended) The preparation of claim 68 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

The preparation of claim 68 wherein the Diltiazem is in the form 70. (Amended) of Diltiazem HCl.

71. (Amended) The preparation of claim 68 wherein the preparation is a diffusion controlled preparation.

72. (Amended) The preparation of class 68 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour

during dissolution.

73. (Amended) The preparation of claim 68 in capsule form.

74. (Amended) The preparation of claim 68 in tablet form.

75. (Amended) The preparation of claim 67 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

76. The preparation of claim 75 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

77.. (Amended) The preparation of clasm 76 wherein the wetting agent assists to maintain the solubility of the Diltiazen in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

78. (Amended) The preparation of claim 77 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

79. (Amended) The preparation of claim 75 wherein the preparation comprises a mixture of the Diltiazem and for pharmaceutically acceptable salt with the wetting

agent and the membrane comprises a water-dispersible of water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

- The preparation of claim 77 wherein the membrane comprises 80. (Amended) Eudragit NE30D and hydroxypropylmethylcellulose.
- The preparation of claim 80 wherein the membrane hydrates the 81. (Amended) core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and/hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

The preparation of claim 77 wherein the Diltiazem is mixed 82. (Amended) with the wetting agent and the membrane comprises an acrylic polymer and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

The preparation of/claim 68 wherein the preparation comprises 83. (Amended) a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

The preparation of claim 83 wherein the dissolution agent is an 84. (Amended) organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric/acid which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

- A method of treatment of a patient's hypertension and/or angina comprising 85. the administration of the preparation of Diltiazem of claim 67 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 86. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 68 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- A method of treatment of a patient's hypertension and/or angina comprising 87. the administration of the preparation of Diltiazem of claim 69 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- A method of treatment of a patient's hypertension and/or angina comprising 88. the administration of the preparation of Diltiazem of claim 70 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- A method of treatment of a patient's hypertension and/or angina comprising 89. the administration of the preparation of Diltiazem of claim 71 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 90. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 72 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 91. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 73 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

- 92. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 74 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 93. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 75 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 94. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 76 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 95. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 77 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 96. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 78 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 97. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 79 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 98. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 80 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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- A method of treatment of a patient's hypertension and/or angina comprising 99. the administration of the preparation of Diltiazem of claim 81 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 100. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 82 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 83 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- A method of treatment of a patient's hypertension and/or angina comprising 102. the administration of the preparation of Diltiazem of claim 84 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

The preparation of claim 68 wherein the preparation contains 103. (Amended) 120 mg of Diltiazem.

104. (Amended) The preparation of clasm 68 wherein the preparation contains 180 mg of Diltiazem.

- 105. (Amended) The preparation of claim 68 wherein the preparation contains 240 mg of Diltiazem.
- 106. (Amended) The preparation of claim 68 wherein the preparation contains 300 mg of Diltiazem.
- The preparation of claim 68 wherein the preparation contains 107. (Amended) 360 mg of Diltiazem.

108. (Amended) The preparation of glaim 68 wherein the preparation contains 420 mg of Diltiazem.

A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 103, 104, 105, 106, 107 or 108 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

A controlled-release Galenical preparation of pharmaceutically 110. (Amended) acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

- into an aqueous medium at the following rates measured using the method of (i) United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - (a) between about 4% and about 8% after 2 hours;
 - (b) between about 16% and about 21% after 4 hours;
 - (c) between about 44% and about 52% after 8 hours;
 - (d) between about 69% and about 76% after 14 hours; and
 - (e) and in excess of about 85% after 24 hours;
- into a buffered medium having a pH about 5.8 at the following rates and/or (ii) measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:
 - (a) between about 4% and about 15% after 2 hours;
 - between about 16% and about 30% after 4 hours; (b)
 - between about 44% and about 62% after 8 hours; (c)
- (d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the

central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins:

 C_{12} to C_{20} fatty acid esters of saccarose, commercialized under the name of sucroesters or under the name of crodesters such as sucrose stearate marketed under the trade name of Crodesta;

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid esters;

polyglycides-glycerides and polyglycides-alcohols esters

Metal salts.

111. (Amended) The preparation of claim 75 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellylose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

- 112. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 110 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
- 113. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 111 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

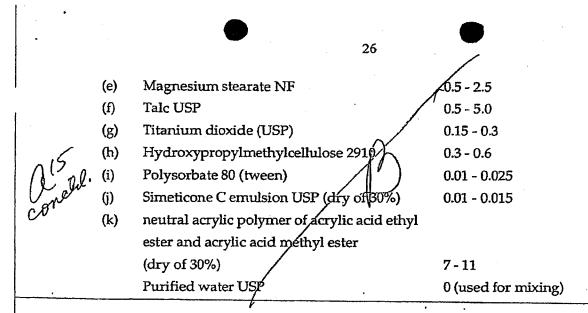
A controlled-release Galenical/preparation of pharmaceutically 114. (Amended) acceptable Diltiazem including the pharmacentically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

- into an aqueous medium at the following rates measured using the method of (i) United States Pharmacopoeia No. XXIII/at 100 rpm in 900 ml of water:
 - (a) · between about 4% and about 8% after 2 hours;
 - (b) between about 16% and about 21% after 4 hours;
 - between about 44% and about 52% after 8 hours; (c)
 - (d) between about 69% and about 76% after 14 hours; and
 - and in excess of about 85% after 24 hours; (e)

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 4% and about 15% after 2 hours;
- (b) between about 16% and about 30% after 4 hours;
- (c) between about 44% and about 62% after 8 hours;
- (d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of midrogranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Piltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

1	% W / V
Diltiazem hydrodhloride	69 - 73
Microcrystalline cellulose	8 - 9.5
Povidone K30	1-2
Sucrose stearate	7 - 8
	Microcrystalline cellulose Povidone K30



115. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 112 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

116. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 4% and about 8% after 2 hours;
- (b) between about 16% and about 21% after 4 hours;
- (c) between about 44% and about 52% after 8 hours;
- (d) between about 69% and about 76% after 14 hours; and
- (e) and in excess of about 85% after 24 hours;

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and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- between about 4% and about 15% after 2 hours; (a)
- (b) between about 16% and about 30% after 4 hours;
- between about 44% and about 62% after 8 hours; (c)
- in excess of about 80% after 24 hours, wherein the preparation (d) comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:
 - (i) in the core,
- 2 mil
- between about 50% and about 85% (% w/w of the total (a) preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
- (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
 - between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 116 to the patient in the

evening for effective treatment of the patient's hypertension and/or angina the next morning.

118. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:



- (a) between about 4% and about 8% after 2 hours:
- (b) between about 16% and about 21% after 4 hours;
- (c) between about 44% and about 52% after 8 hours;
- (d) between about 69% and about 76% after 14 hours; and
- (e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 4% and about 15% after 2 hours;
- (b) between about 16% and about 30% after 4 hours;
- (c) between about 44% and about 62% after 8 hours;
- in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:
 - (i) in the core.

- (a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
- (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

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- (ii) in the membrane,
 - (c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- 119. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 118 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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120. (Amended) The preparation of claim 77 wherein the preparation is a tablet and the tablet comprises micrographiles in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

121. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 120 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

122. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form-of Diltiazem, with excipients, to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:



(i) in the core,

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- (a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
- (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
 - between about 0.1% and about 2% of the total preparation of (c) water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - (d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

- The preparation of claim 122 wherein the microgranules are in capsule form. 123.
- The preparation of claim 122 wherein the microgranules are in tablet form. 124.
- The preparation of claim 122, 123 or 124 wherein the core and 125. (Amended) membrane comprise:
 - (i) in the core,
 - between about 69% and about 73% (% w/w of the total (a) preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - between about 7% and about 8% wetting agent (% w/w of the (b) total preparation);

together with suitable adjuvants; and

- (ii) in the membrane,
 - (c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and
 - between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.
- The preparation of claim 122, 123 or 124 wherein the core and membrane 126. comprise:

% W/W

(a) Diltiazem hydrochloride 69 - 73

- (b) Microcrystalline cellulose (Avicel ph101)8 - 9.5
- Povidone K30 (c)

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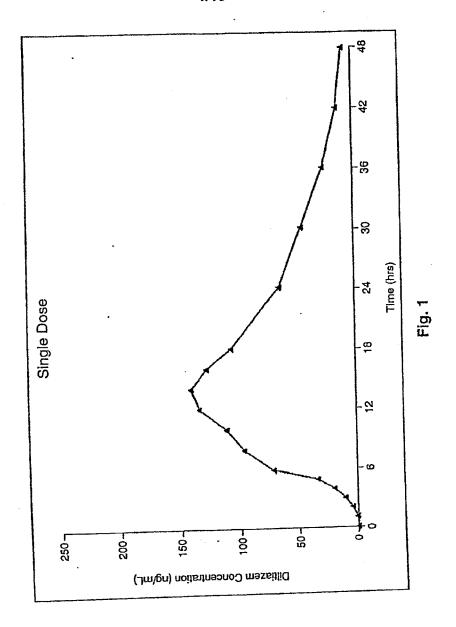
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	Eudragit NE30 D (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

127. (Amended) The preparation of claim 122 or 124 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

(2D

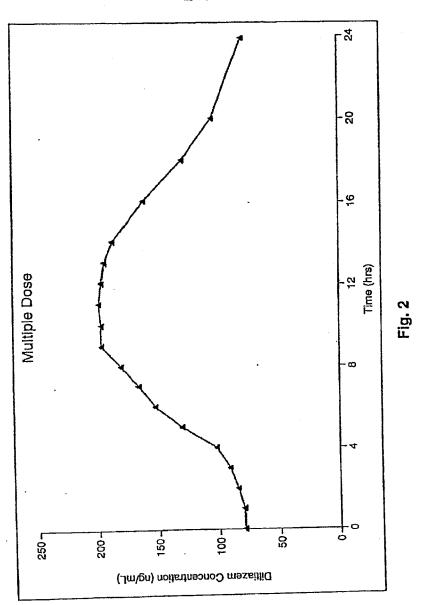
128. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 122, 123 or 124 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

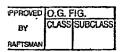
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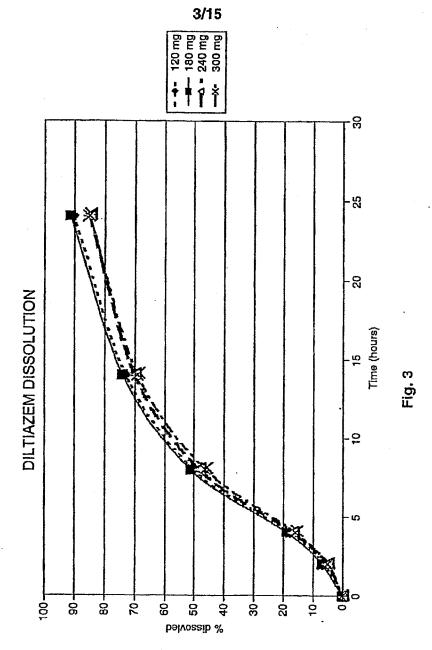


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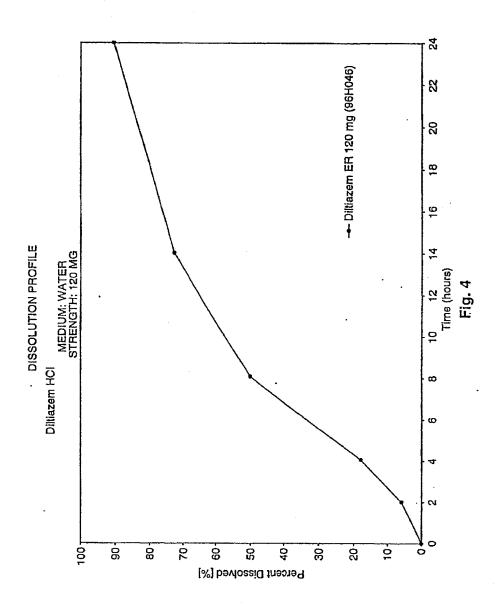


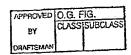


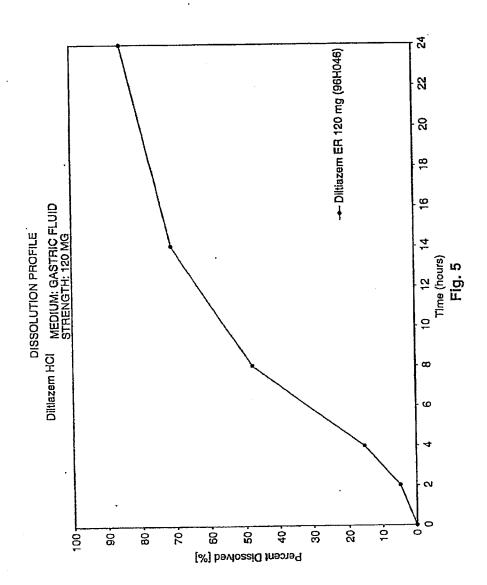




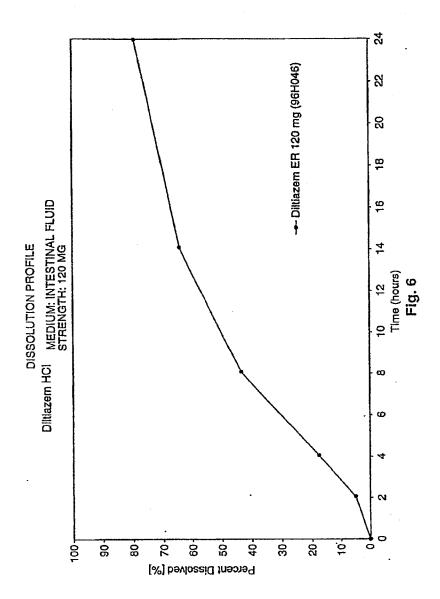
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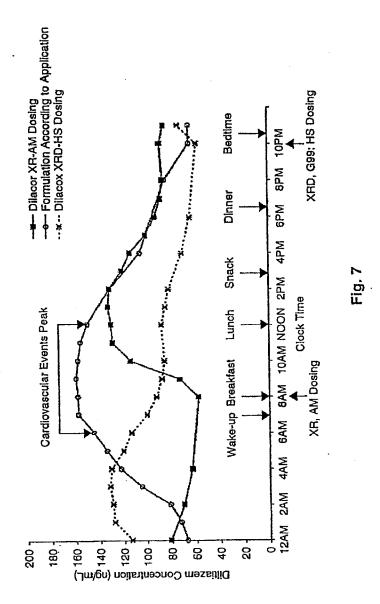


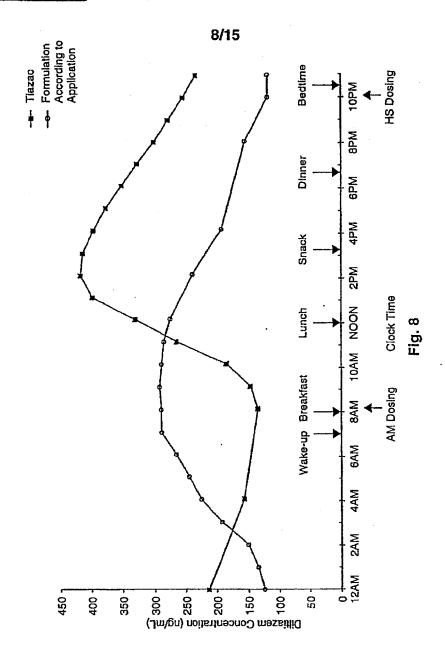


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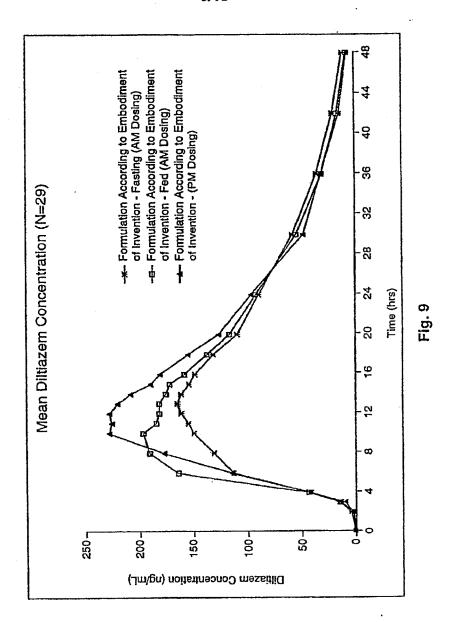


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10/15

Diltiazem AUCt PK Summary

	For	mulation i	According to	Embodimen	d of inventi	ion		
							Morning	
	Morning			ng Fed		Dosing		Night/Morning
Subject	AUCE	Log AUC		Log AUCt	AUCI	Log ÄUCI	Ratio '	Ratio
2	1730.75	7.45	2547.15	7.88	1987.11	7.59	1.53	1.15
3	2712.98	7.91	2336.67	7.76	3248.94	6.09	0.85	1.20
4	2688.34	7.90	1907.61	7.55	2892.21	7.97	0.71	1.08
5	4192.37	8.34	4108.85	8.32	4702.33	8.45	0.98	1.12
6	3074.51	8.03	2887.98	7_97	3900.06	8.27	0.94	1,27
7	1629.81	7.40	1847,56	7.52	2723.36	7.91	1.13	1.67
8	941.10	6.85	1970.97	7.59	1835.11	7.51	2.09	1.95
9	3144.13	8.05	3462.59	8.15	2923.86	7.98	1.10	0.93
10	2074.94	7.54	2997,45	8.01	4028.83	8.30	1.44	1.94
11	3653.96	8.20	2771,53	7.93	3464.72	8.15	0.76	8.95
12	2684,22	7.90	3790.43	8.24	3141,47	8.05	1,41	1.17
13	3352.69	8.12	3751.95	8.23	3708.83	8.22	1.12	1.11
14	2988.61	8.00	3655.60	8.21	3141.05	8.05	1.23	1.05
15	6796.97	8.82	8204.22	9.01	7578.33	8.93	1.21	1.11
16	2873.70	7.96	4644.79	8.44	4192.09	8.34	1.62	1.46
17	4468,33	8.40	4222.55	8.35	3762.50	8.23	0.94	0.84
18	5654.29	8.54	5635.72	8.64	7159.38	8.88	1.00	1.27
19	4944.07	8.51	5107.44	8.54	4812,20	8.48	1.03	0.97
20	2986.73	8.00	2988,34	8.00	2791,23	7.93	1.00	0.93
21	2908.88	7.98	3314.12	8.11	4389.98	8.39	1.14	1.51
22	4270.43	8.35	3790.06	8.24	3631.01	5.20	0.89	0.85
23	6150.18	8.72	6092.56	8.71	7478.22	8.92	0.99	1.22
25	2926.46	7.98	5633.64	8.54	4839.10	8.4B	1.93	1.85
26	3928.61	8.28	4614.43	8.44	4359,77	8.38	1.17	1.15
27	3637.94	8.20	4587,48	8.43	4063.15	8.31	1.26	1,12
28	4177.76	8.34	4945,31	8.51	6689.14	8.81	1.18	1.60
29	3609.69	8.19	2720.67	7.91	2163.20	7.68	0.75	0.60
30	4483.17	8,41	5222.54	8,56	5587.50	8.63	1.16	1.25
32	4058.04	8.31	3531.47	8.17	3082,87	8.03	0.87	0.76
Mean	3542.88	8.10	3910,40	8.21	4078.57	8,25	1.15	1.20
SD	1304,23	0.41	1431.24	0,36	1554.69	0.37	0.33	0.33
CY	35.81	5.08	36.60	4.43	38.12	4.46	28.23	27.33
Median	3352,69	8.12	3751.95	8.23	3762.50	8.23	1.12	1.12
Geo Mean	3292.B3	8.09	3671.24	B.20	3818.30	5.24	1.11	1.16
Fed/Fasting	g Ratio (Mo	ming Dos	ing)		Night/Mo:	ming Ratio		
Ratio of Mo	ans	1.10			Ratio of P	leans	1.15	
Ratio of Ga		1.77	#			Seo Means	1.16	
Avg of Indi			f			dividual Ratios	1.20	

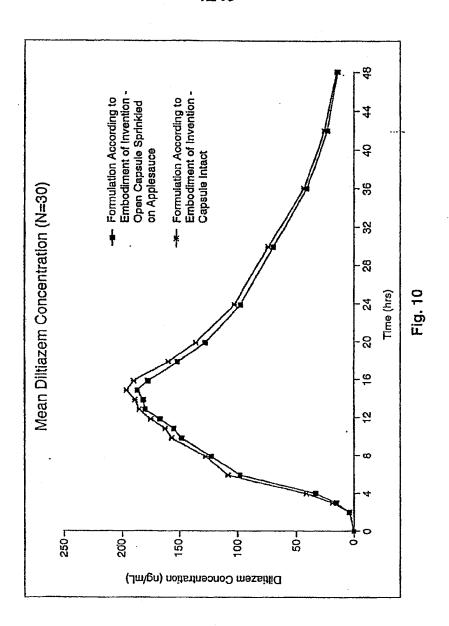
Fig. 9A

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8-0 jeef 7-10	Morning Fed. Morning Fed. Might Desking Morning Fed. Might Desking Morning Fed. Might Desking Might Morning Radio Might Mi				Formulati	on Accord	ling to Emb	Formulation According to Embodiment of Invention	ventlon			₩ W	Noming	
Comman Track Corner Log Crimat Crimat Corner Nation 1877 623 110 120 12457 655 654 655	Comman Track Cornix Log Crimit (1986) 5.8		ž	Sea Man	No		Momins Fe	•		Night Dost	Č	7	Frs -	MghtMoming
100 197,71 523 13,0 143,84 457 1400 141,71 524 15,0 143,84 457 1400 141,71 524 14,0 141,44 525 15,4 14,0 141,44 525 120,4 14,0 141,44 525 120,4 14,0	100 197,71 523 13.0 143,84 457 1480 1480 1481	Sciblant.	Tare	Canar	Log Cmax		Critex	Log Cmix	TIME	CHEE	Log Cmax	Z	ş	Ratio
11.0 (12.04 4.8) 10.0 24.657 6.51 0.80 0.80 0.80 0.80 0.80 0.80 0.80 0.8	11.0 (12.04 4.8) (10.0 24.657 8.5) (0.09 1.08 1.09 1.09 1.09 1.09 1.09 1.09 1.09 1.09		Ş	DA AG	4 59	10.0	187.71	523	<u>.</u>	143.64	4.97		8	1,48
10. 110.00 110.00 170.00 10.00	100 116.60 4.75 10.0 191.44 6.25 0.89 4.1 8.0 195.80 5.26 10.0 191.44 6.25 6.1 10.0 195.80 5.26 10.0 195.84 0.89 6.2 12.0 12.14 5.10 178.87 5.19 1.34 6.2 12.0 178.87 5.19 1.34 6.3 10.0 195.81 5.12 178.87 5.19 1.35 6.4 10.0 196.84 5.42 10.0 178.87 5.19 1.15 6.0 196.84 5.42 10.0 196.84 5.28 1.17 6.0 196.85 5.24 10.0 196.84 5.24 1.17 6.0 196.85 5.24 10.0 196.84 5.34 1.25 6.0 196.85 5.24 10.0 196.84 5.34 1.25 6.0 196.85 5.24 10.0 197.29 5.29 1.17 6.0 196.85 5.24 10.0 197.20 5.29 1.17 6.0 10.0 196.85 5.20 13.0 197.20 5.29 6.1 10.0 175.76 5.17 13.0 2.24 6.2 10.0 175.76 5.17 13.0 2.24 6.3 10.0 175.76 5.17 13.0 2.24 6.4 10.0 2.24 6.5 10.0 175.76 5.17 13.0 13.14 6.5 10.0 175.76 5.17 13.0 13.14 6.6 10.0 2.24 6.7 10.0 2.24 6.8 10.0 175.76 5.17 13.0 13.14 6.9 10.0 2.25 6.0 10.0		5	1.78 CA	7	11.0	123.04	4.83	0	246,57	5.51	ø	8	1.6.
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11.0 119.210 4.75 11.0 175.82 4.89 1.48 1.	110 1102 1102 110 1102 110 1102 1102 11		2 5	3	1 2 7	44.0	121.64	4.80	120	179.67	5.19	-	¥	1.88
1,0	1,0	٠.	2	2			119.30	4.78	15.0	133,35	4.89	-	.82	2.03
10	10	۰ د	9	00.00		: 4	700	E 10	12.0	175.62	5.17	<u></u>	8	1.33
11.0 164.64 5.04 14.0 164.66 5.21 0.73 17. 10.0 201.45 5.31 11.0 174.69 5.46 1.47 18. 10.0 201.45 5.31 11.0 174.69 5.46 1.47 18. 10.0 205.35 5.32 13.0 187.32 5.23 1.47 18. 10.0 204.32 5.50 13.0 187.32 5.23 1.43 18. 10.0 244.32 5.50 13.0 187.32 5.43 18. 10.0 244.32 5.50 13.0 234.40 5.44 18. 10.0 247.24 5.32 13.0 234.40 5.44 18. 10.0 247.24 5.33 13.0 247.04 5.51 18. 10.0 247.29 5.33 13.0 247.04 5.51 18. 10.0 247.29 5.43 13.0 247.04 5.51 18. 10.0 247.29 5.43 13.0 247.04 5.51 18. 10.0 247.29 5.43 13.0 247.04 5.51 18. 10.0 247.29 5.43 13.0 247.24 5.43 18. 10.0 247.29 5.43 13.0 247.24 5.43 18. 10.0 247.29 5.43 13.0 247.24 5.43 18. 10.0 247.29 5.43 13.0 247.24 5.43 18. 10.0 247.29 5.43 14.1 24.34 18. 10.0 247.29 14.1 24.34 18. 10.0 247.2	110 16464 5.04 14.0 16436 5.21 0.73 177 10.0 201,45 5.31 14.0 174,89 6.46 180 201,45 5.32 11.0 174,89 6.46 180 201,45 5.32 11.0 174,89 6.46 180 201,45 5.32 11.0 174,89 6.46 180 201,45 5.32 11.0 174,89 6.46 180 201,45 5.32 11.0 201,91 6.42 180 201,45 5.40 11.0 201,91 6.42 180 201,45 5.40 11.0 201,91 6.41 180 201,45 5.40 11.0 211,40 11.4 180 201,40 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 5.40 11.0 211,40 11.4 180 201,40 5.40 5.40 11.0 211,40 11.4 180 201,40 5.40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 5.40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 211,40 11.4 180 201,40 5.40 11.0 21.4 180 201,40 5.40 11.0 21.4 180 201,40 5.40 11.0 21.4 180 201,40 5.40 11.0 21.4 180 201,40 5.40 11.0 21.4 180 201,40 5.40 11.0 21.4 180 201,40 5.40 11.0 21.4 180 201,40 5.40 11.0 21.4 180 201,40 5.40 11.	> !	2	182.40	9 1	3 1	10 804		130	9	5.28		27.	5.00
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127 13.0 16073 5.08 12.0 128.94 4.87 0.75 12.0 244.58 5.50 10.0 138.84 5.82 1.01 12.1 24.58 5.50 10.0 238.84 5.82 1.01 12.2 24.5 0.31 11.8 242.46 5.42 0.40 13.2 24.3 0.018 5.32 11.8 242.48 5.42 0.40 13.2 24.3 0.018 5.32 11.8 262.48 5.42 1.28 13.1 0.0 204.08 5.32 11.9 208.78 1.33 1.43 1.20 13.1 0.0 204.08 5.32 11.9 208.78 1.43 1.20 13.1 0.0 204.08 5.32 11.9 208.78 1.43 1.23 13.1 0.0 204.08 5.32 11.9 208.78 1.43 1.23 13.1 0.0 204.08 5.32 11.9 208.78 1.33 13.1 0.0 204.08 1.33 1.41 1.33 13.1 0.0 204.08 1.34 1.35 13.2 0.0 204.08 1.34 1.35 13.3 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0	127 13.0 160.73 5.08 12.0 128.94 4.87 0.75 13.0 160.73 5.08 12.0 128.94 4.87 0.75 13.0 12.0 244.28 5.50 10.0 338.94 5.62 11.01 11.2 12.0 244.28 5.30 11.0 238.94 5.62 11.01 11.2 11.2 11.2 21.3 3.3 11.8 224.28 0.31 1.8 224.3 0.31 1.8 224.3 0.31 1.8 224.3 0.31 1.8 224.3 0.31 1.8 224.3 11.0 208.79 1.3 11.0 208.79 1.3 11.0 11.0 11.0 11.0 11.0 11.0 11.0	7	2 5			-	238 10	5.48	11.0	364,02	5,95	~	80	1.78
12.0 244.58 5.50 10.0 338.84 5.82 1.01 17.2 15.0 244.58 5.50 11.0 238.30 5.44 17.2 15.0 245.89 5.32 11.0 238.30 5.44 17.3 10.2 215.53 5.33 11.8 226.26 5.42 1.29 17.3 2.5 64.83 0.31 15.8 86.39 0.30 17.3 2.5 64.83 0.31 14.1 44.82 6.48 0.34 17.0 10.0 204.09 5.32 11.0 208.79 3.34 1.30 17.1 9.0 208.00 5.32 11.0 208.79 3.34 1.30 17.1 19.0 208.00 5.32 11.0 208.79 3.34 1.30 17.3 228.29 8.41 1.35 2.3 Ratio of Means 2.4 Ratio of Means 2.5 Ratio of Means 2.5 Ratio of Means 2.7 Ratio of Means 2.8 Ratio of Medical Ratio 2.9 Ratio of Medical Ratio 2.1 Ratio of Means 2.2 Ratio of Medical Ratio 2.3 Ratio of Medical Ratio 2.4 Ratio of Medical Ratio 2.5 Ratio of Medical Ratio 2.7 Ratio of Medical Ratio 2.8 Ratio of Medical Ratio 2.9 Ratio of Medical Ratio of Medical Ratio 2.9 Ratio of Medical Ratio o	1.2 24,58 5.50 10.0 338.54 5.82 1.01 1.2 10.2 24,58 5.50 11.0 231.33 8.44 1.2 10.2 215.33 5.33 11.8 242.48 5.42 1.3 24.3 5.33 11.8 242.48 5.42 1.0 2.04.09 5.32 11.0 231.33 8.42 1.1 9.9 206.00 5.32 11.0 208.79 3.34 1.10 9.9 206.00 5.32 11.1 228.79 3.34 1.20 1.11 9.9 206.00 5.32 11.1 228.79 3.34 1.23 1.24 Ratio of Means 1.25 Ratio of Means 1.27 Ratio of Means 1.29 Agroi Individual Ration 1.41	8 8	2 :	27017	, e	Ş	160.73	80.5	12.0	128.94	4.87	٥	.75	0.60
12. 16.2 204.09 6.32 11.0 231.33 6.44 0.67 1.29 1.20 24.3 5.33 11.8 24.24 6 4.42 1.29 1.32 24.3 50.09 6.32 11.0 231.33 6.44 6.42 0.40 1.32 24.3 50.09 6.32 11.6 80.39 0.36 0.40 1.32 24.3 50.09 6.32 11.6 208.79 3.34 1.30 1.30 1.30 1.30 1.30 1.30 1.30 1.30	7.2 15.0 204.09 5.32 11.0 231.33 5.44 0.67 7.2 10.2 215.53 5.33 11.6 231.33 5.44 7.2 2.6 64.85 5.33 11.6 232.46 5.42 1.29 7.2 24.3 50.89 5.83 14.7 208.79 5.34 1.30 7.3 20.0 5.32 11.0 208.79 3.34 1.30 7.3 20.0 5.32 11.0 208.79 3.34 1.30 7.3 208.00 5.32 11.0 208.79 3.34 1.33 7.3 208.00 5.32 11.0 208.79 3.34 1.33 7.3 Radio of Mesins 7.3 Radio of Mesins 7.4 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7.5	₹ ;	2 :	41.4			BN 776	5	Ç	338 64	5.82	-	5	1.39
1.12 10.2 215.53 5.33 11.6 242.46 8.42 1.29 1.32 24.3 0.34 1.6 86.39 0.36 0.40 1.32 24.3 0.34 1.41 4.32 6.43 6.39 0.40 1.32 24.3 0.30.9 6.32 11.0 208.79 8.34 1.20 1.11 9.9 206.30 9.32 11.5 226.53 8.41 1.33 1.32 Ratio of Means 1.35 2.3 Avg of individual Ratio 1.41	1.12 10.2 21.5.53 5.33 11.6 22.2.46 8.4.2 1.29 1.37 2.56 6.4.35 0.31 1.6 86.38 0.36 0.40 1.37 2.4.3 50.0.9 5.32 14.5 46.32 6.4.8 50.49 1.30 10.0 204.00 5.32 14.0 208.79 3.34 1.30 1.11 9.9 206.00 5.32 14.5 228.73 8.41 1.20 1.21 Ratio of Means 1.38 1.33 Avg of individual Ratios 1.41 1.29 Fig. 98	3 8	2 5	24.00	, K	3 5	204.09	5.32	1.0	231.33	4.	a	191	0,78
1.2 10.2 21553 5.33 11.8 242.46 5.42 1.29 1.37 2.5 64.25 0.31 11.6 828.36 0.35 0.40 1.32 2.43 50.09 6.83 14.5 208.39 6.38 50.09 1.10 9.0 204.09 6.32 11.5 228.63 8.41 1.20 1.11 9.0 208.00 5.32 11.5 228.63 8.41 1.23 1.21 Ratio of Menns 2.3 Avg of individual Ratio 1.41	1.2	;	?	7	ť	2		•						
25 243 50.31 1.6 86.39 0.36 0.40 27 243 30.09 6.32 14.1 40.82 6.38 30.89 27.0 (1.0) 20.40 6.32 11.0 208.78 3.34 1.20 27.1 9.9 206.00 6.32 11.4 228.83 6.41 1.23 28 Ratio of Means 1.38 29 Ratio of Means 1.35 29 Ratio of Gee Réans 1.35 29 Avg of individual Ratio 1.41	23 243 30.05 6.83 6.43 0.40 23 243 30.05 6.83 14,5 66.38 0.38 30.08 241 9.0 204.08 6.32 14,0 206.78 9.34 1.20 241 9.0 206.00 6.32 14,0 206.78 9.34 1.20 25 Ratio of Mesins 1.39 25 Ratio of Mesins 1.35 26 Avg of individual Ration 1.41	Xex	12.6	178.45		10.2	215.53	5,33	11.8	242.48	5.42	*	Ą.	7
22 24.3 30.09 6.53 14.1 44.92 6.58 30.69 5.70 10.0 204.09 6.32 11.0 208.79 3.34 1.20 5.71 9.9 208.00 6.32 11.0 208.79 8.44 1.23 FRUID OF Means 2.1 RAUGO PIMENTS 2.2 Avg of individual Raugo 1.41	132 24.3 30.09 5.83 14.5 44.8 4.88 30.89 140 206.00 5.32 14.0 206.79 3.34 1.20 141 9.9 206.00 5.32 14.5 226.73 5.41 141 9.9 206.00 5.32 14.5 226.73 5.41 142	ç		64.85		2.5	64.85	0.31	9	96.98	970	•	ş	ก
120 10.0 204.00 6.3.2 11.0 208.76 8.3.4 1.20 1.11 9.9 206.00 5.3.2 11.5 226.63 8.41 1.33 Night/Morning Ratio Ratio of Means 1.36 Avg of individual Ratios 1.41	120 10.0 204.08 6.3.2 11.0 208.78 5.34 1.20 1.11 9.9 206.00 5.3.2 11.5 228.65 5.41 1.33 Night/Morning Ratio Ratio of Means 1.35 Ratio of Goe Niens 1.35 Avg of individual Ration 1.41	5	19.8	34.86	7.52	24.3	30.09	5.83	14.5	40.62	6.5 8	Ħ ·	9.0	27.83
1.31 9.9 206.00 5.32 11.5 228.53 8.41 1.23 NighWhoming Ratio Ratio of Means 1.38 Avg of individual Ratios 1.41	1.31 9.9 206.00 5.32 11.5 228.53 8.41 1.33 1.31 Night/Morning Ratio 2.1 Ratio of Means 1.35 2.3 Avg of individual Ratios 1.41 Fig. 9B	5		164.78		10.0	204.08	532	5.0	208.78	7	-	2	รู
NightMoming Ratio 2.1 Ratio of Means 2.3 Ratio of Gao Means Avg of individual Ratios	NightMoming Ratio 21 Ratio of Menne 23 Ratio of Geo Menne Avg of Individual Ration Fig. 9B	Geo Meso	7	167.47		6	206,00	5.32	£	226.63	7	_	R	1.35
Night/Morning Railo Railo of Means 23 Railo of Means Ang of Individual Railos	Hight/Morning Ratio Ratio of Means Ratio of Groo Means Avg of individual Ratios													
1.21 Ratio of Means 1.23 Avg of Individual Ratios	1.21 Ratio of Means 1.23 Ratio of Means 1.29 Avg of Individual Ration Fig. 9B	PedFasting	Ratio (A	Morning Da	(Bulg)				Night	oming Ratic				
1.21 Ratio of Means 1.23 Avg of Individual Ratios	1.23 Ratio of Geo Mans 1.29 Avg of Individual Ratios Fig. 9B								,	;		•		
1.29 Avg of Indvidual Ballon	1.29 Avg of Individual Ration Fig. 9B	Ratio of Me	15		121				Ratio of	Houns Occ Kinns		100		
i	Fig.	Patie of Ot Avg of Ingh	o Meana Idual Ra	flos	7 7				Avgof	ndividual R	100	3		
i i	Fig. 9B													
	בס. תם							i	E					

APPROVED	O.G. FIG.			
87	CLASS	SUBCLASS		
DRAFTSMAN				

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APPROVED		
BY	CLASS	SUBCLASS
DRAFTSMAN		

93.35 93.00 85.73 86%-99%

AUC:

AUC:

Ratio of Moans % 94.16 Ratio of Means % 83.98 Avg of Individual Ratios % 90% C.I. Intra-CV 13.47% Intra-CV

Imax

Open Capsule Sprinkled on Applessauce 73.7 hours Capsules Intact 13.5 hours

PK Summary (N=30)

Dilitazem PK

Fig. 10A

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Diltiazem AUCt Results

Formulation According to Embodiment of Invention

	Open Capsules Sprinkled on Applesauce (A)		Capsul	e Intact (B)	(A:B)
Subject	AUCt	Log Cmax	AUCI	Log Cmax	Ratio
i	3937.18	8.26	3251.62	8.09	1.21
2	3782.89	8.24	5502.18	·· 8.61 · · ·	0.69
3	1616.35	7.39	2358.22	7.77	0.69
4	8209.44	9.01	7954.29	8.98	1.03
5	2171.26	7.68	2452.78	7.80	0.89
6	5710.90	8.65	7082.30	8.87	0.81
7	1983.56	7,59	2624.03	7.87	0.76
8	3862.46	8.26	3114.53	8.04	1.24
9	6069.65	8.71	4585.60	8.43	1.32
10	3907.33	8.27	6393.14	8.76	0.61
11	3842.58	8.25	4292.30	8.36	0.90
12	4873.82	8.49	6493.87	8.78	0.75
13	2707.85	7.90	3922.90	8.27	0.69
14	2553.27	7.85	2159.88	7.68	1.18
15	2042.47	7.62	2902.70	7.97	0.70
16	4650.14	8.44	4769.32	8,47	0.98
17	3705.72	8.22	3464.89	8.15	1.07
19	7881.69	8.97	6851.45	8.83	1.15
21	6151.00	8.72	6292.65	8.75	0.98
22	2138,64	7.67	1933.52	7.57	1.11
23	3983.50	8.29	5177.74	8.55	0.77
24	3939.51	8.2B	3517.56	8.17	1.12
25	2318.36	7.75	2016.26	7.61	1.12
27	2061.09	7.63	1928.02	7.56	1.07
28	2871,31	7.96	3312.87	8.11	0.87
29	4305.14	8.37	3559.57	8.18	1.21
30	3190.17	8.07	3565.88	8.18	0.89
31	3422.16	8.14	3012.17	8.01	1.14
33	4906.47	8.50	5206.52	8.56	0.94
34	2969.19	8.00	3255.28	8.09	0.91
				2.00	0.01
Mean	3859.17	8.17	4098.47	8.24	0.96
SD	1664,90	0.42	1708.24	0.41	0.20
CV	43.14	5.10	41.68	5.03	20.69
Median	3817.74	8.25	3538.57	8.17	0.96
Geo Mean	3546.16	8.16	3773.43	8.23	0.94
TestiRef Ra	atio				
Ratio of Ma	ans %	94.16			
Ratio of Ge	o Means %	93.98			
	vidual Ratios	0.96			
80% C.L		88%-99%			
Intra-CV		13.47%			

Fig. 10B

APPROVED	O.G. FiG.			
BY	CLASS	SUBCLASS		
DRAFTSMAN				

Diltiazem Cmax Results

Formulation According to Embodiment of Invention

Open Capsule Sprinkled on Applesauce (A)		Capsule Intact (B)			(A:B)		
Subject	Tmax	Cmax	Log Cmax	Tmax	Cmax	Log Cmax	Ratio
1 1	13.0	184.35	5.22	13.0	228.99	5,43	0.81
2	14.0	192.44	5.26	12.0	285.72	5.66	0.67
3	13.0	103.87	4.64	12.0	127.07	4.84	0.82
4	10.0	372.93	5.92	B.0	298.05	5.70	1.25
5	14.0	107.71	4.68	16.0	147.84	5.00	0.73
6	13.0	244.67	5.50	15.0	315,48	5.75	0.7B
7	14.0	115.23	4.75	16.0	135,27	4.91	0.85
8	13.0	257.26	5.55	15.0	179.11	5.19	1.44
9	8.0	232.12	5.45	10.0	194.37	5.27	1.19
10	16.0	172.20	5.15	15.0	281.81	5.64	0.61
11	13.0	177,41	5.18	8.0	181.17	5.20	0.98
12	13.0	225.55	5.42	10.0	327.23	5.79	0.50
13	15.0	135.86	4.91	15.0	213.37	5.36	0.64
14	15.0	154.65	5.04	14.0	135.94	4.91	1.14
15	12.0	114.81	4.74	15.0	181.80	5.20	0.63
16	15.0	294.21	5.68	13.0	296.58	5.69	0.99
17	15.0	187.32	5.23	15.0	183.62	5.21	1.02
19	16.0	385,36	5.95	15.0	376.57	5.93	1.02
21	15.0	318.06	5.76	10.0	276.15	5.62	1.15
22	14.0	114.40	4.74	14.0	97.24	4.58	1.18
23	12.0	260.20	5.56	12.0	346.74	5.85	0.75
24	14.0	211,61	5,35	16.0	202.88	5.31	1.04
25	14.0	155.98	5.05	15.0	125.66	4.83	1,24
27	16.0	79.66	4.38	16.0	67.35	4.21	1.18
28	16.0	124.76	4.83	16.0	165.01	5.11	0.76
29	15.0	225.58	5.42	10.0	164.02	5.10	1.38
30	14.0	166.54	5.12	15.0	165.41	5.11	1.01
31	15.0	134.14	4.90	14.0	135.19	4.91	0.89
33	13.0	282.10	5.64	16.0	275.33	5.62	1.02
34	10.0	118.88	4.78	15.0	155.15	5.04	0.77
Mean	13.7	195.00	5.19	13.5	208,90	5,27	0.96
SD	1.9	80.09	0.41	2.5	80.27	0.41	0.23
CA	13.8	41.07	7.83	18.3	38.43	7.73	24.25
Median	14.0	180.88	5.20	15.0	182.71	5.21	0.99
Geo Mean	13.5	180.09	5.18	13.3	193.65	5.25	0.93
Tost/Ref Ra	dio						
Ratio of Me			93.35				
	o Means %		93.00				
	vidual Ratios		0.95				
90% C.L	٠.		86%-99%				
Intra-CV			16.07%				

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Fig. 10C

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on May 2, 2007, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

> Richard L. Horwitz POTTER ANDERSON & CORROON LLP

and that I caused copies to be served upon the following in the manner indicated:

BY HAND AND E-MAIL

Richard L. Horwitz POTTER ANDERSON & CORROON LLP 1313 North Market Street P.O. Box 951 Wilmington, DE 19899-0951 rhorwitz@potteranderson.com

BY EMAIL

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/s/ Karen Jacobs Louden				
klouden@mnat.com				